

Document made available under the Patent Cooperation Treaty (PCT)

International application number: PCT/IB2005/000687

International filing date: 17 March 2005 (17.03.2005)

Document type: Certified copy of priority document

Document details: Country/Office: IN
Number: 562/Del/2005
Filing date: 16 March 2005 (16.03.2005)

Date of receipt at the International Bureau: 29 August 2005 (29.08.2005)

Remark: Priority document submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b)



World Intellectual Property Organization (WIPO) - Geneva, Switzerland
Organisation Mondiale de la Propriété Intellectuelle (OMPI) - Genève, Suisse



राष्ट्रपति जनसे



INTELLECTUAL
PROPERTY INDIA

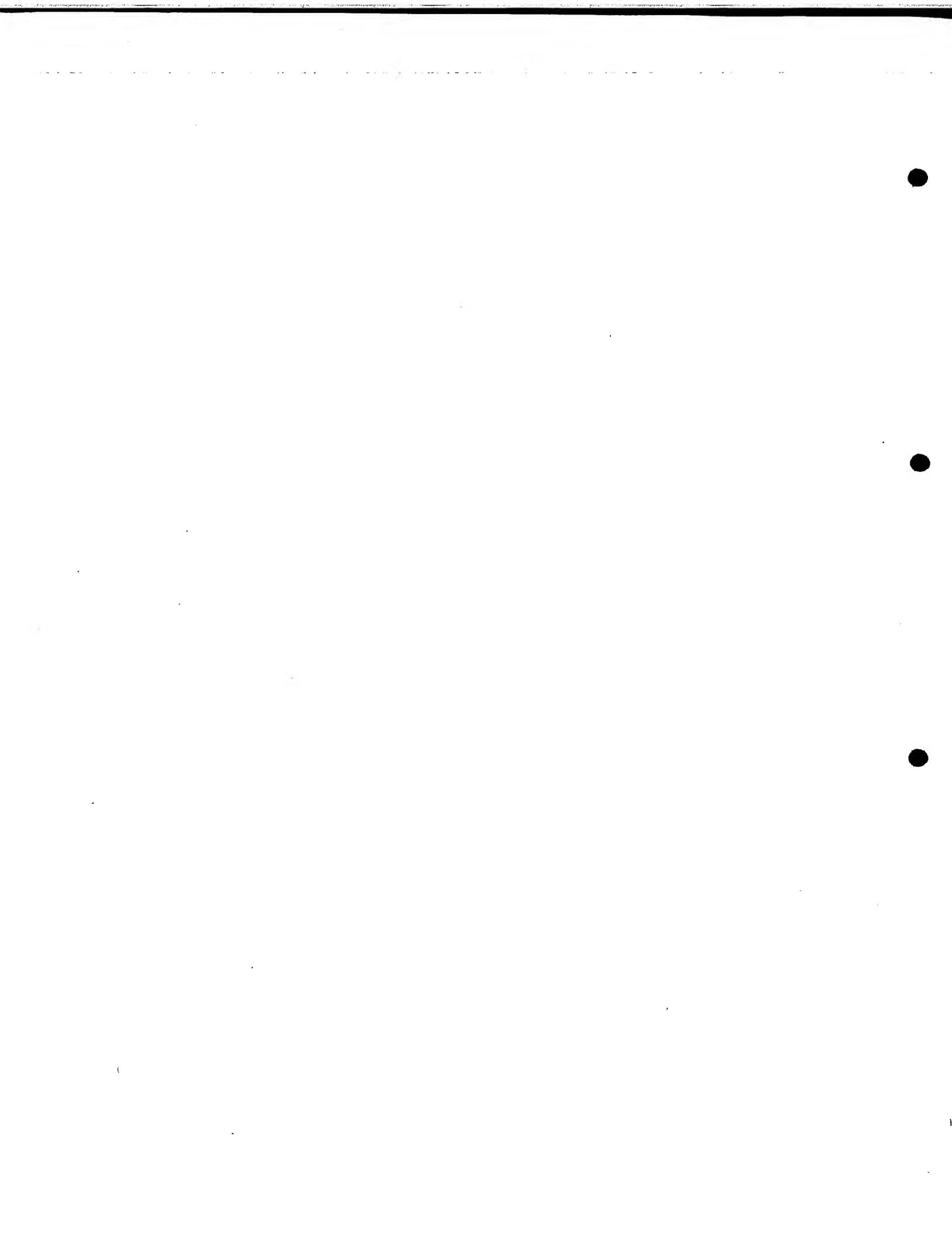
GOVERNMENT OF INDIA
MINISTRY OF COMMERCE & INDUSTRY
PATENT OFFICE, DELHI BRANCH
PLOT NO.32, SECTOR-14, DWARKA
NEW DELHI - 110 075.

I, the undersigned being an officer duly authorized in accordance with the provision of the Patent Act, 1970 hereby certify that annexed hereto is the true copy of the Application, Complete Specification and Drawing Sheets filed in connection with Application for Patent No.562/Del/2005 dated 16th March 2005.

Witness my hand this 9th day of August 2005.

A handwritten signature in black ink, appearing to read 'S.K. Pangasa'.

(S.K. PANGASA)
Assistant Controller of Patents & Designs



FORM 1
THE PATENT ACT 1970
(39 of 1970)
&
The Patents Rules, 2003

**APPLICATION FOR GRANT
OF PATENT**
(See section 7, 54 and 135 and Rule 20(1))

(FOR OFFICE USE ONLY)

Application No. 16 MP 105

Filing Date: _____

Amount of Fee Paid: Rs. _____

CBR No. _____

Signature: _____

1. APPLICANT (S)
RANBAXY LABORATORIES LIMITED, an Indian Company, incorporated under the Companies Act. 1956. Corporate Office at 19, Nehru Place, New Delhi – 110019, India.
2. INVENTOR (S)
YATENDRA KUMAR, SARIDI MADHAVA DILEEP KUMAR, SWARGAM SATHYANARAYANA,
All Indian Nationals. of Ranbaxy Laboratories Limited, Plot No. 20, Sector-18, Udyog Vihar Industrial Area, Gurgaon – 122001 (Haryana), India.
3. TITLE OF THE INVENTION
“CRYSTALLINE FORM OF ATORVASTATIN HEMI CALCIUM”
4. ADDRESS FOR CORRESPONDENCE OF APPLICANT/ AUTHORIZED AGENT IN INDIA:
DR. B. VIJAYARAGHAVAN
Associate Director – Intellectual Property
Ranbaxy Laboratories Limited
77-B, IFFCO Road, Sector – 18, Udyog Vihar Industrial Area,
Gurgaon–122001, Haryana, India.
Telephone Nos.: (0124) 2343126, 5194271
Fax Nos. (0124) 2342027, 5016855
5. PRIORITY PARTICULARS OF THE APPLICATION(S) FILED IN CONVENTION
COUNTRY: NOT APPLICABLE
6. PARTICULARS FOR FILING PATENT COOPERATION TREATY (PCT) NATIONAL PHASE APPLICATION: NOT APPLICABLE
7. PARTICULARS FOR FILING DIVISIONAL APPLICATION: NOT APPLICABLE
8. PARTICULARS FOR FILING PATENT OF ADDITION: 491/DEL/2004 dated 17.03.2004.

9. DECLARATIONS:

(i) Declaration by the Inventor(s):

We, the above named inventor(s) is/are the true and first inventor(s) for this invention and declare that the applicant herein, **Ranbaxy Laboratories Limited**, Corporate Office at 19, Nehru Place, New Delhi – 110019, India, is our assignee or legal representative.

Date	Signature(s)	Name (s)
<u>16.03.05</u>	<u>Yatendra Kumar</u>	Yatendra Kumar
<u>16.03.05</u>	<u>Saridi Madhava Dileep Kumar</u>	Saridi Madhava Dileep Kumar
	<u>Swargam Sathyanarayana</u>	Swargam Sathyanarayana

(ii) Declaration by the applicant(s) in the convention country:

We, the applicant, in the convention country declare that the applicant herein is our assignee or legal representative.

Date : _____

For Ranbaxy Laboratories Limited


(SUSHIL KUMAR PATAWARI)
Company Secretary

(iii) Declaration by the Applicant(s) :

We, the applicant (s) hereby declare (s) that :-

- ◊ We are in possession of the above-mentioned invention.
- ◊ The provisional / complete specification relating to the invention is filed with this application.
- ◊ The invention as disclosed in the specification uses the biological material from India and necessary permission from the competent authority shall be submitted by us before the grant of the patent to us.
- ◊ There is no lawful ground of objection to the grant of the Patent to us.
- ◊ We are the assignee or legal representative of true and first inventors.
- ◊ The application or each of the applications, particulars of which are given in Para-5 was the first application in convention country / countries in respect of our invention.
- ◊ We claim the priority from the above mentioned application(s) filed in convention country/ countries and state that no application for protection in respect of the invention had been made in a convention country before that date by us or by any person from which we derive the title.
- ◊ Our application in India is based on International application under Patent Cooperation Treaty (PCT) as mentioned in Para-6.
- ◊ The application is divided out of our application particulars of which are given in Para-7 and pray that this application may be treated as deemed to have been filed on _____ under sec.16 of the Act.
- ◊ The said invention is an improvement in or modification of the invention particulars of which are given in Para-8.

10. FOLLOWING ARE THE ATTACHMENTS WITH THE APPLICATION:

- (a) Provisional specification / Complete specification
- (b) Complete specification (in conformation with the international applications)/as amended before the International Preliminary Examination Authority (IPEA), as applicable (2 copies), No. of Pages _____ No. of claims _____
- (c) Drawings (in conformation with the international application)/as amended before the International Preliminary Examination Authority (IPEA), as applicable (2 copies), No. of sheets _____
- (d) Priority documents
- (e) Translation of priority documents / Specification/International Search Report
- (f) Statement and undertaking on Form 3
- (g) Power of Authority
- (h) Declaration of inventorship on Form 5
- (i) Sequence listing in electronic form
- (j) _____

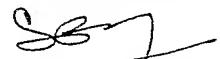
Fee Rs. _____ in Cash/Cheque/Bank Draft bearing No. _____

Date _____ on HDFC Bank Limited, Gurgaon.

We hereby declare that to the best of our knowledge, information and belief the fact and matters stated herein are correct and we request that a patent may be granted to us for the said invention.

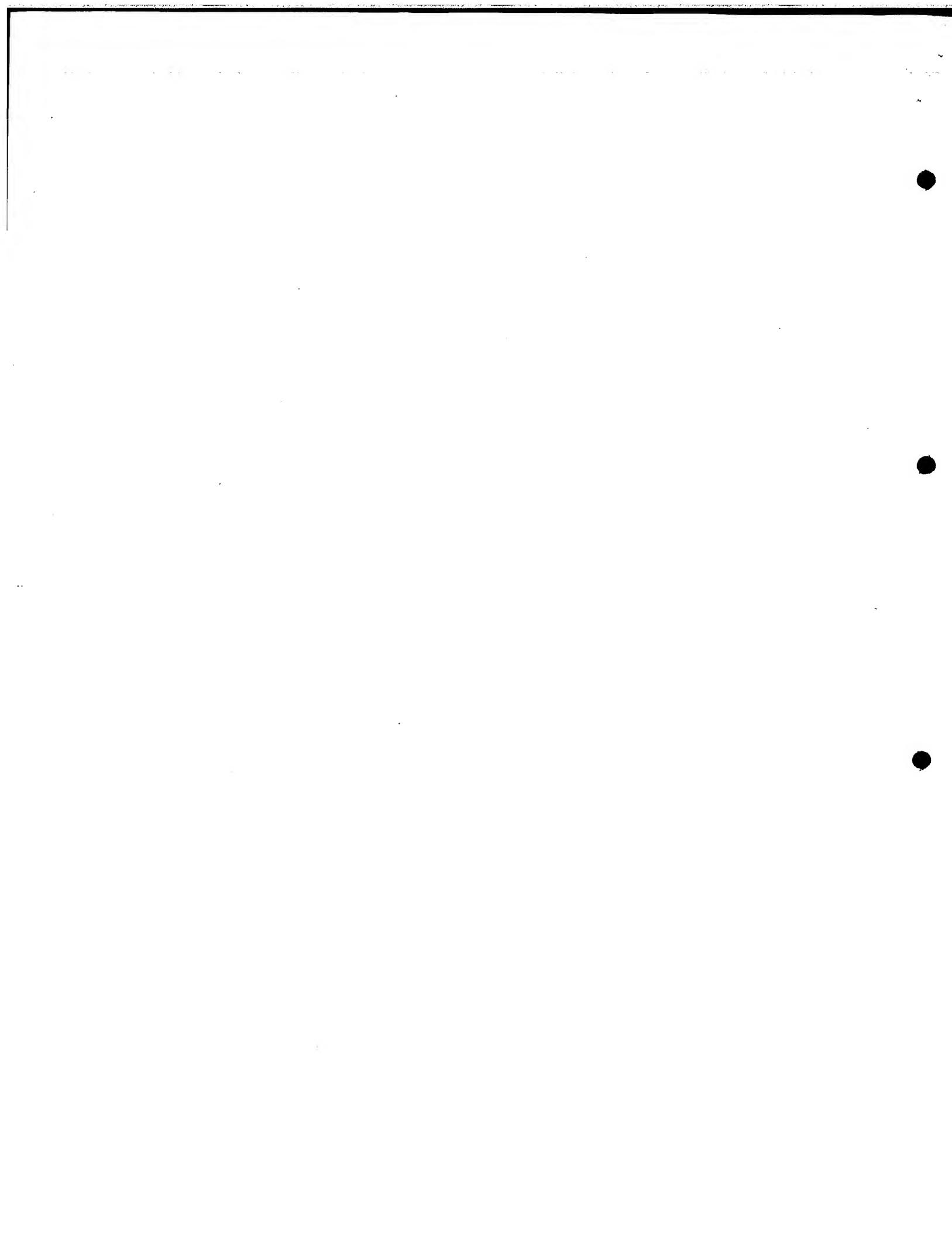
Dated this 16TH day of March, 2005.

For Ranbaxy Laboratories Limited


(SUSHIL KUMAR PATAWARI)
Company Secretary

To

The Controller of Patent
The Patent Office
New Delhi



FORM 2

053205

16/02/2006

The Patents Act, 1970

(39 of 1970)

&

The Patent Rules, 2003

COMPLETE SPECIFICATION
(See Section 10 and Rule 13)

**CRYSTALLINE FORM OF ATORVASTATIN
HEMI CALCIUM**

RANBAXY LABORATORIES LIMITED
CORPORATE OFFICE : PLOT NOS. 89, 90, 91, SECTOR -32,
GURGAON – 122001, HARYANA

A Company incorporated under the Companies Act, 1956.

The following specification particularly describes and ascertains the nature of this invention and the manner in which it is to be performed:

This application claims the priority of Indian patent application, 491/DEL/2004 entitled, "Process for the production of atorvastatin calcium in amorphous form" filed on Mar, 17, 2004.

Field of the Invention

The present invention relates to novel crystalline form of atorvastatin hemi calcium and hydrates thereof. The method of preparation of the novel crystalline form of atorvastatin hemi calcium and hydrates thereof, its pharmaceutical compositions and method of using compositions to treat mammals suffering from hypercholesterolemia are also provided.

Background of the Invention

Atorvastatin is known by the chemical name [*R*-(*R*^{*}, *R*^{*})]-2-(4-fluorophenyl)-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1*H*-pyrrole-1-heptanoic acid. The hemi-calcium salt of atorvastatin is useful as an inhibitor of the enzyme 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMG-CoA reductase) and is thus useful as a hypolipidemic and hypocholesterolemic agent.

U.S. Patent Nos. 5,273,995; 5,003,080; 5,097,045; 5,103,024; 5,124,482; 5,149,837; 5,155,251; 5,216,174; 5,245,047; 5,248,793; 5,280,126; 5,397,792; and 5,342,952, disclose various processes and intermediates for preparing atorvastatin. Several processes have been reported for the preparation of amorphous form of atorvastatin calcium in U.S. Patent Nos. 6,528,660 and 6,613,916; U.S. Patent Application Publication Nos. 2002/183378 and 2003/109569; and International (PCT) Patent Applications WO 01/28999, WO 02/57228, WO 02/83637, WO 02/83638, WO 03/18547 and WO 03/68739.

Several crystalline forms of atorvastatin hemi-calcium have been reported in the literature. However, there is still a need to produce Atorvastatin hemi calcium in a reproducible, pure and crystalline form to enable formulations to meet exacting pharmaceutical requirements and specifications. Furthermore, it is economically desirable that the product is stable for extended periods of time without the need for specialized storage conditions. Accordingly, the present invention is directed to the novel crystalline Form of Atorvastatin hemi calcium salt herein referred as Form R.

Summary of the Invention

In one aspect, crystalline form R of atorvastatin hemi calcium and hydrates thereof is provided.

In another aspect, process for preparing the crystalline form R of atorvastatin hemi calcium and hydrates thereof is provided comprising dissolving crude atorvastatin hemi calcium in tetrahydrofuran and methanol and recovering novel Form R atorvastatin hemi calcium and hydrates thereof.

Isolation of form R of atorvastatin hemi calcium or hydrates thereof may be accomplished by precipitation, cooling, or a combination thereof.

In a further aspect, a pharmaceutical composition comprising the crystalline form R of atorvastatin hemi calcium and hydrates thereof, along with pharmaceutically acceptable excipients, diluents and carriers is provided.

In yet another aspect, a method for treatment or prevention of hyperlipidemia, hypercholesterolemia, alzheimer's disease atherosclerosis, xanthoma and in synergism with other drugs for treatment of phytosterolemia lipase deficiency and the like, which comprises administering to a mammal in need thereof, an effective amount of crystalline form R of atorvastatin hemi calcium and hydrates thereof is provided.

In yet another aspect, the present invention also relates to a process of preparation for amorphous atorvastatin hemi calcium comprising dissolving crystalline Form R of atorvastatin hemi calcium in a solvent, and adding the resulting solution to an anti-solvent.

Fig. 1 is an X-ray diffraction spectrum of crystalline form R of atorvastatin hemi calcium.

Fig.2 is an IR spectrum of crystalline form R of atorvastatin hemi calcium using potassium bromide pellets.

Fig.3 is a DSC graph of crystalline form R of atorvastatin hemi calcium.

Detailed Description of the Invention

The term "crude atorvastatin hemi calcium" refers to atorvastatin hemi calcium prepared by any of the methods known in the art. Crude atorvastatin hemi calcium may also be obtained as a solution, for example from a reaction mixture resulting directly from a reaction in which crude atorvastatin hemi calcium is formed. Crude atorvastatin hemi calcium may exist in any of the polymorphic form reported in the literature and may have unreacted compounds, side product and other impurities.

The mixture of crude atorvastatin, tetrahydrofuran and methanol may be heated upto reflux. The mixture may also be filtered before heating to remove undissolved material. Isolation of form R of atorvastatin hemi calcium or hydrates thereof may be accomplished by precipitation, cooling, or a combination thereof.

Precipitation may occur on addition of an anti solvent. An anti-solvent is a liquid that does not dissolve atorvastatin hemi calcium. Anti solvent may be added at a temperature of about 50 to 70°C. The precipitation of form R of atorvastatin hemi calcium and hydrates thereof takes place using water as anti solvent.

Tetrahydrofuran, methanol and water may be used in the volume ratio 1:1:4 to obtain crystalline Form R of atorvastatin calcium of high purity. Water may be added at a temperature of about 60 to 65 °C.

Crystalline Form R of atorvastatin hemi calcium and hydrates thereof may be isolated by cooling the mixture to a temperature of about 20 to 40°C and stirring at the same temperature for several hours before filtration or centrifugation.

Crystalline Form R of atorvastatin hemi calcium may be characterized by strong X-ray diffraction peaks at about 8.62, 10.16 and 19.32 degrees two-theta and weak peaks at about 3.6, 8.24, 18.12, 18.36, 20.44, 20.82, 21.22 and 23.82 degrees two-theta. The term "about" means the values provided with a margin of \pm 0.2 degrees two-theta. Crystalline Form R of atorvastatin hemi calcium may also be characterized by its IR and DSC.

Crystalline Form R of atorvastatin hemi calcium and hydrates thereof may be converted into the amorphous form of atorvastatin hemi calcium or hydrates thereof by dissolving crystalline Form R of atorvastatin hemi calcium in a solvent, and adding the resulting solution to an anti-solvent. Examples of solvents include ketones such as acetone and methyl isobutyl ketone; esters such as ethyl acetate and isopropyl acetate; chlorinated hydrocarbons such as methylene chloride and ethylene dichloride; cyclic ethers such as dioxane and tetrahydrofuran; alcohols such as methanol, ethanol and isopropanol; nitriles such as acetonitrile; dipolar aprotic solvents such as dimethylsulfoxide and dimethylformamide; and mixtures thereof with water. Examples of anti-solvents include hydrocarbons, such as cyclohexane, hexanes, heptanes, petroleum ethers, toluene, xylene and the like; dialkyl ethers such as diethyl ether, diisopropyl ether, and the like; and can readily be determined by one ordinarily skilled in the art.

An antioxidant may be added to the atorvastatin hemi calcium solution to obtain stabilized, amorphous atorvastatin hemi calcium. Examples of suitable antioxidants include butylated hydroxyanisole, butylated hydroxytoluene and tertiary-butylated hydroquinone.

The term 'stabilized atorvastatin hemi calcium' means the hemi-calcium salt of atorvastatin having a level of purity, which is provided and maintained through the use of antioxidants. Stabilized, amorphous atorvastatin calcium can be obtained with purity of at least 97%, for example when determined by high performance liquid chromatography (HPLC) analysis. In general, stabilized, amorphous atorvastatin calcium having a purity of at least 99% may be obtained. In some particular embodiments, stabilized, amorphous atorvastatin calcium having a purity of at least 99.5% may be obtained.

Crystalline Form R of atorvastatin hemi calcium or hydrates thereof may be converted into the amorphous form by methods known in the art such as U.S. Patent Nos. 6,528,660 and 6,613,916; International (PCT) Patent Applications WO 01/28999, WO 03/99785, WO 03/78379, WO 03/18547 and WO 02/57228; and U.S. Patent Application Publication No. 2002/183378, which are incorporated herein by reference.

Crystalline Form R of atorvastatin hemi calcium or hydrates thereof may be formulated into pharmaceutical compositions. The pharmaceutical composition comprises Crystalline Form R of atorvastatin hemi calcium or hydrates thereof as an active ingredient along with one or more pharmaceutically acceptable carriers, diluents or excipients. The Crystalline Form R of atorvastatin hemi calcium or hydrates thereof may be conventionally formulated into tablets, capsules, suspensions, dispersions, injectables and other pharmaceutical forms. Any suitable route of administration may be employed for example peroral or parental.

There is also provided a method of treating hypercholesterolemia and hyperlipidemia comprising administering a therapeutically effective amount of Crystalline Form R of atorvastatin hemi calcium or hydrates thereof.

Crystalline Form R of atorvastatin hemi calcium or hydrates thereof may be used in the manufacture of a medicament for the treatment or prevention of hyperlipidemia, hypercholesterolemia, Alzheimer's disease, atherosclerosis, xanthoma and in synergism with other drugs for treatment of phytosterolemia lipase deficiency and the like.

In the following section embodiments are described by way of example to illustrate the process disclosed herein. However, these do not limit the scope of the present invention. Several variants of these examples would be evident to persons ordinarily skilled in the art.

Example 1: Preparation of amorphous [R-(R*,R*)]-2-(4-fluorophenyl)- β,δ -dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino) carbonyl]-1H-pyrrole-1-heptanoic acid, calcium salt (2:1) (Atorvastatin Calcium Amorphous)

**(4R-cis)-1,1-dimethylethyl-6-{2-[2-(4-fluorophenyl)-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)-carbonyl]-1H-pyrrol-1yl]ethyl}-2,2-dimethyl-1,3-dioxane-4-acetate
(Compound H)**

A mixture of (4R-cis)-1,1-dimethylethyl-6-(2-aminoethyl)-2,2-dimethyl-1,3-dioxane]-4-acetate (9 Kg, 32.96 moles), (\pm)-4-fluoro- α -(2-methyl-1-oxopropyl)- γ -oxo- N,β -diphenylbenzenebutaneamide (13.33 Kg, 31.93 moles), n-heptane (90 L), tetrahydrofuran (22.5 L), toluene (22.5 L) and pivalic acid (2.18 Kg, 21.30 moles) was heated to reflux temperature for

about 40 hrs. The reaction was monitored for completion by HPLC. The reaction mass was cooled and diluted with toluene. The reaction mixture was then washed initially with aqueous sodium hydroxide solution (0.5 N), then with aqueous hydrochloric acid solution (0.5 N) and followed by brine (10%). The organic layer was treated with activated carbon, and filtered through a hyflo filter. The organic layer was concentrated to 10% of the total volume under vacuum. Isopropyl alcohol (34 L) was then added, and the solvent recovered under vacuum, followed by repeated addition of isopropyl alcohol and solvent recovery under vacuum. The residue was dissolved in isopropyl alcohol and de-ionized water (45 L) was added till turbidity appeared. Further de-ionized water (60 L) was added gradually. The precipitated product was filtered, washed with a mixture of isopropyl alcohol and de-ionized water (2:1) and dried to get the title compound (16.2 Kg, 24.77 moles, 94% by HPLC). The crude product was purified by dissolving in isopropyl alcohol (128 L) at 50 to 55 °C, concentrating the solution and cooling the residual mass slowly under stirring. The solid thus obtained was filtered, washed with chilled isopropyl alcohol and dried at 40 to 45 °C to give pure Compound H (13.2 Kg, 20.20 moles, purity: 99% by HPLC).

[R-(R*,R*)]-1,1-Dimethylethyl-2-(4-fluorophenyl)-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoate (Compound I)

To a solution of Compound H (10 Kg, 15.29 moles) in methanol (217 L), 1 N hydrochloric acid solution (21 L, 16.04 moles) was added at 20-26 °C in 15 minutes. The reaction mixture was stirred at the same temperature until the reaction was complete (about 6 hours, monitoring by HPLC).

[R-(R*,R*)]-2-(4-Fluorophenyl)-β, δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)-carbonyl]-1H-pyrrole-1-heptanoic acid, sodium salt (Atorvastatin Sodium)

The pH of the reaction mixture obtained above was adjusted to about 12 by adding 10% w/v aqueous sodium hydroxide solution at 25-30 °C and the resulting mixture was stirred for about 6 hours at 25-30 °C. The progress of the reaction was monitored by HPLC. The pH of the reaction mixture was monitored and maintained at about 12 throughout the course of the reaction by adding 10% w/v aqueous sodium hydroxide solution. After the reaction was complete, the mass was filtered and concentrated to about 84 L.

Crude [R-(R*,R*)]-2-(4-fluorophenyl)- β,δ -dihydroxy-5-(1-methylethyl)-3-phenyl-4-[phenylamino]-carbonyl]-1*H*-pyrrol-1-heptanoic acid, calcium salt (2:1) (Atorvastatin Calcium Crude)

De-ionised water (89 L), methanol (19 L), and methyl tertiary butyl ether (60 L), were added to the concentrated reaction mass obtained above with continuous stirring. The layers were separated. The aqueous layer was washed with methyl tertiary butyl ether and filtered through a sparkler filter. The filtrate was collected in a reactor and its pH adjusted to 7.9-8.1 with 6 N hydrochloric acid. This mixture was heated to 48 °C.

To this mixture, an aqueous solution of calcium acetate (1.33 Kg, 8.41 moles) in water (48 L) was added slowly and heated to 51 °C. The contents were stirred at 51-54 °C until a clear solution was obtained. Crystalline atorvastatin calcium Form I seeds (77g) were added and stirred. Methyl tertiary butyl ether was recovered under reduced pressure. The temperature was raised to 58 °C and de-ionised water (11 L) was added. The contents were cooled to 50 °C and a second lot of atorvastatin calcium Form I seeds (33g) were added. The contents were further cooled slowly to 30 °C over a period of 3-4 hours and filtered. The wet cake was washed with a mixture of methanol and de-ionised water. The material was dried at 45-50 °C to yield 8 Kg of atorvastatin calcium having a purity of 97.5% determined by HPLC.

Pure Crystalline Atorvastatin Calcium

The crude product obtained above was charged to a reactor containing methanol (16 L) and tetrahydrofuran (40 L). The contents are stirred to get a clear solution and filtered through a sparkler filter followed by washing over hyflo bed with methanol (32 L).

The filtrate was heated to 65 °C and refluxed for 30-60 minutes. To this, de-ionised water (about 120 L) was added slowly over a period of 1-2 hours until turbidity appeared. At the onset of turbidity, crystalline atorvastatin calcium Form I seeds (8g) were added. The contents were stirred for 30 minutes at 68-72 °C and de-ionised water (about 40L) was added. The contents were cooled to 50 °C and atorvastatin calcium Form I seeds (24g) were added with continuous stirring. The contents were further cooled to 35 °C and stirred for 5 hours at 33-35 °C and then filtered. The wet cake was washed with a mixture of tetrahydrofuran, methanol and de-ionized

water (volume ratio 1:1:4) and then dried at 50-55 °C under reduced pressure to yield 7.36 Kg of crystalline atorvastatin calcium.

Preparation of Crystalline Atorvastatin Calcium (Form-I)

The above dried product was added to a reactor containing de-ionized water (108.8 L) and methanol (19.2 L). The contents were stirred for 10 minutes and heated to 45 °C. To this, crystalline atorvastatin calcium form I seeds (730g) were added and the mixture was stirred at 40 °C to 45 °C until the IR spectrum of the sample was comparable with the seed crystals. The contents were filtered and washed with a mixture of de-ionized water and methanol (volume ratio 6:1). The wet cake was dried at 50-55 °C to yield 7.2 Kg of crystalline atorvastatin calcium having a purity of 99.7% determined by HPLC.

Atorvastatin Calcium Amorphous

Tetrahydrofuran (16.38 L) was added to crystalline atorvastatin calcium Form I (6.3 Kg, 5.2moles) obtained above followed by butylated hydroxyanisole (63 g, 0.5 moles). The contents were stirred for 30 minutes at 20 to 25 °C to get a solution. This solution was filtered over a hyflo bed followed by washing of the hyflo bed with tetrahydrofuran (2.52 L), and the filtrate was collected. The filtrate was added slowly over a period of 4 to 5 hours to cyclohexane (189 L) at 25 °C. The contents were stirred for 60 minutes, centrifuged and washed with cyclohexane. The material was dried under vacuum at 60 °C to 70 °C for 12 hours to yield 5.67 Kg of amorphous atorvastatin calcium having a purity of 99.54% determined by HPLC.

Example 2: Preparation of Atorvastatin Calcium Amorphous

Tetrahydrofuran (10 L) was added to atorvastatin calcium Form I (1 Kg) obtained as per Example 1 above, followed by butylated hydroxyanisole (3 g). The contents were stirred for 15 minutes at 20 to 25 °C to get a solution. This solution was filtered over hyflo bed followed by washing of the hyflo bed with tetrahydrofuran (0.4 L), and the filtrate was collected and concentrated to a volume of about 3 L at 62 to 70 °C. The solution was cooled to 20 °C and added slowly over a period of 4 to 5 hours to cyclohexane (30 L) at 20 to 23 °C. The contents were stirred for 60 minutes and filtered. The wet cake was washed with cyclohexane. The material was dried under vacuum at 60 °C to 70 °C for 12 hours to yield 0.9 Kg of amorphous atorvastatin calcium having a purity of 99.45% determined by HPLC.

Preparation of Crystalline Atorvastatin Calcium (Form-II)

EXAMPLE 3

A mixture of methanol (180 ml) and de-ionized water (120 ml) was added to crystalline atorvastatin calcium form I (15 g) at room temperature. The temperature was raised to 25 °C, seeds of crystalline atorvastatin calcium form II (1.5 g) were added, and the suspension was stirred at 25 °C. The suspension became very thick after about 24 hours and a mixture of methanol (90 ml) and de-ionized water (60 ml) was added to resume stirring. The suspension was further stirred at 25 °C for another 24 hours and then filtered. The filtered solids were dried under reduced pressure at 70 °C for 48 hours to get 14.7 g of crystalline atorvastatin calcium. The XRD spectrum of the product matched with that of Form-II of atorvastatin calcium.

EXAMPLE 4

A mixture of methanol (1.2 L) and de-ionized water (800 ml) was added to crystalline atorvastatin calcium Form I (100 g) at room temperature. The temperature was raised to 45 °C slowly, seeds of crystalline atorvastatin calcium form II (10 g) were added, and the suspension stirred at 45 °C. The suspension became very thick after about 24 hours and a mixture of methanol (600 ml) and de-ionized water (400 ml) was added to resume stirring. The suspension was again warmed to 45 °C and further stirred at the same temperature for another 24 hours and then filtered. The filtered solids were dried under reduced pressure at 70 °C for 48 hours to get 98 g of crystalline atorvastatin calcium. The XRD spectrum of the product matched with that of Form-II of atorvastatin calcium.

EXAMPLE -5

Preparation of Crystalline Form R of atorvastatin hemi calcium

The crude atorvastatin hemi calcium was charged to a reactor containing methanol (16 L) and tetrahydrofuran (40 L). The contents were stirred to get a clear solution and filtered through a sparkler filter, followed by washing over hyflo bed with methanol (32 L). The filtrate was heated to 65°C and refluxed for 30-60 minutes. To this, de-ionized water (about 120 L) was added slowly over a period of 1-2 hours until turbidity appeared. The contents were stirred for 30 minutes at 68-72°C and de-ionized water (about 40L) was added. The contents were cooled to 35°C and stirred for 5 hours at 33-35°C and then filtered. The wet cake was washed with a mixture of tetrahydrofuran, methanol and de-ionized water (volume ratio 1:1:4) and then dried at 50-55°C under reduced pressure to yield 7.33 Kg of crystalline atorvastatin hemi calcium.

Powder XRD, IR and DSC were similar to those shown in Fig. 1, 2 and 3 respectively of the accompanied drawings.

EXAMPLE-6

Preparation of Atorvastatin hemi calcium Amorphous

Tetrahydrofuran (480 ml) was added to Crystalline Form R of atorvastatin hemi calcium obtained above in Example 1 (60 g), followed by butylated hydroxyanisole (0.6 g). The contents were stirred, de-ionized water (24 ml) was added and the mixture was stirred for 15 minutes at 20 to 25°C to get a clear solution. Molecular sieves (240 g, Siliporite NK30 AP® powdered) were added to the solution and the mixture was stirred for 2 hours at 20 to 25 °C. This solution was filtered through a molecular sieves bed, followed by washing of the bed with tetrahydrofuran (120 ml). The filtrate was collected and concentrated to a volume of about 210 ml at 60 to 70°C. The concentrated solution was cooled to 25°C and added slowly over a period of 2 hours to cyclohexane (1800 ml) at 22 to 25°C under moderate stirring. The contents were stirred vigorously for 30 minutes at the same temperature and filtered. The wet cake was washed with cyclohexane (60 ml). The material was dried under reduced pressure at 60°C to 70°C for 6 hours to yield 54 g of amorphous atorvastatin hemi calcium.

Example 7: Preparation of Crystalline Atorvastatin Calcium (Form II)

A mixture of methanol (1.2 L) and de-ionized water (800 ml) was added to crystalline atorvastatin calcium obtained above in example 5 (100 g) at room temperature. The temperature was raised to 45 °C slowly, seeds of crystalline atorvastatin calcium form II (10 g) were added, and the suspension stirred at 45 °C. The suspension became very thick after about 24 hours and a mixture of methanol (600 ml) and de-ionized water (400 ml) was added to resume stirring. The suspension was again warmed to 45 °C and further stirred at the same temperature for another 24 hours and then filtered. The filtered solids were dried under reduced pressure at 70 °C for 48 hours to get 98 g of crystalline atorvastatin calcium. The XRD spectrum of the product matched with that of Form-II of atorvastatin calcium.

Example 8: Preparation of Atorvastatin Calcium Amorphous

Tetrahydrofuran (10 L) was added to atorvastatin calcium crystalline Form II (1 Kg) followed by butylated hydroxyanisole (3 g). The contents were stirred for 15 minutes at 20 to 25 °C to get a solution. This solution was filtered over a hyflo bed followed by washing of the hyflo bed with tetrahydrofuran (0.4 L), and the filtrate was collected and concentrated to a volume of about 3 L at 62 to 70 °C. The solution was cooled to 20 °C and added slowly over a period of 4 to 5 hours to cyclohexane (30 L) at 20 to 23 °C. The contents were stirred for 60 minutes and filtered. The

wet cake was washed with cyclohexane. The material was dried under vacuum at 60 °C to 70 °C for 12 hours to yield 0.9 Kg of amorphous atorvastatin calcium having a purity of 99.5% determined by HPLC.

Example 9: Atorvastatin Calcium Amorphous

Methanol (100 mL) was added to atorvastatin calcium form II (10 g). The contents were stirred for 40 minutes at 20 to 25° C to get a clear solution. Butylated hydroxyanisole (0.1g) was then added and the mixture stirred for 30 minutes. Methanol (50 ml) was then recovered at 40° C under reduced pressure in 30 minutes. The solution was cooled to 20 to 25° C and added slowly over a period of one hour to cyclohexane (300mL) at 20 to 30° C. The solution was stirred for 1 hour at 25° C. The obtained clear solution was concentrated to a volume of about 300 L at 60 to 70° C (approximately 50 ml methanol was distilled out). The obtained suspension was then cooled to 20 to 25° C with stirring in 30 minutes and filtered. The wet cake was washed with cyclohexane. The material was dried under vacuum at 60 °C to 70 °C for 1 hour to yield 9.0 g of amorphous atorvastatin calcium.

Example 10: Preparation of (*4R-cis*)-1,1-dimethylethyl-[6-(2-aminoethyl)-2,2-dimethyl-1,3-dioxan-4-yl] acetate (Compound F)

(*R*)-1,1-dimethylethyl-6-cyano-5-hydroxy-3-oxohexanoate (Compound C)

n-Butyl lithium and diisopropylamine are mixed at -40 °C for the formation of lithium diisopropylamine. 1,1-Dimethylethyl acetate (Compound B) in tetrahydrofuran is then added at -50 °C and the mixture stirred at -20 to 25 °C for 1 hour. The reaction mixture is further cooled to -50 °C and (*R*)-ethyl-4-cyano-3-hydroxybutanoate is added maintaining temperature at -20 to -25 °C and kept at the same temperature for 2 hours. The reaction is monitored for completion by thin layer chromatography. The reaction is quenched with a 2 N solution of hydrochloric acid and the product was extracted with ethyl acetate, washed with water and brine followed by complete evaporation of solvent to get the title compound which is taken to the next step without further purification.

[*R*-(*R*^{*}, *R*^{*})]-1,1-dimethylethyl 6-cyano-3, 5-dihydroxyhexanoate Compound D)

To a mixture of tetrahydrofuran and methanol containing (*R*)-1,1-dimethylethyl-6-cyano-5-hydroxy-3-oxohexanoate (Compound C) is added diethyl methoxyborane slowly at -80 to -90 °C and stirred for 30 minutes at the same temperature. Sodium borohydride is added in lots maintaining temperature at -80 to -90 °C and stirred for 5 hours at -80 to -90 °C. After completion of reaction, the temperature is slowly raised to 0 °C then to room temperature in 2

hours, and the reaction quenched with glacial acetic acid slowly in 30 minute while maintaining temperature between 0 to 40 °C. The mixture is concentrated to approximately 20% of total volume. Methanol is added and recovered to remove borane derivatives. The product is extracted with ethyl acetate, washed with water and then brine. The organic layer is concentrated to approximately 20% of original volume. Tetrahydrofuran is then added and recovered completely under reduced pressure to get the title compound as a concentrated mass, which is taken to the next step.

(4*R*-*cis*)-1,1-Dimethylethyl-[6-cyanomethyl-2,2-dimethyl-1,3-dioxan]-4-acetate (Compound E)

A mixture of 2,2-dimethoxy propane containing-[*R*-(*R*^{*},*R*^{*})]-1,1-dimethylethyl-6-cyano-3,5-dihydroxyhexanoate (Compound D), acetone and methanesulfonic acid is stirred for 3 to 4 hours at 29 to 30 °C and the reaction monitored for completion by thin layer chromatography. The reaction is then quenched with 5% w/v aqueous sodium bicarbonate solution slowly to adjust pH to about 7 and extracted with ethyl acetate. The organic layer is concentrated and the solvent recovered completely under reduced pressure. The residue is crystallized with hexane to get the title compound as a crude product, which is recrystallized with methanol and water to get the pure compound.

(4*R*-*cis*)-1,1-Dimethylethyl-[6-(2-aminoethyl)-2,2-dimethyl-1,3-dioxan-4-yl]acetate (Compound F)

Pure(4*R*-*cis*)-1,1-dimethylethyl-[6-cyanomethyl-2,2-dimethyl-1,3-dioxan]-4-acetate (Compound E) dissolved in ammonia saturated methanol is hydrogenated in the presence of activated Raney nickel by applying hydrogen pressure of 4.5 to 5 kg/cm² at room temperature under stirring for 4 to 12 hours. The reaction is monitored for completion by gas chromatography. The catalyst is filtered through hyflo bed and concentrated to recover methanol completely under reduced pressure to get the title compound.

Example 11: Preparation of crystalline atorvastatin calcium form-I seed

Part A - Preparation of Crude Atorvastatin Calcium

[*R*-(*R*^{*},*R*^{*})]-1,1-Dimethylethyl-2-(4-fluorophenyl)-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1*H*-pyrrole-1-heptanoate (Compound I)

To a solution of Compound H (57g) in methanol (1.71L), 1 N hydrochloric acid solution (116 mL) was added drop wise at 20-25 °C in 15 minutes. The reaction mixture was stirred at the same temperature for about 5 hours, and monitored by TLC (hexane:ethanol :: 6:4). 1 N hydrochloric acid solution (10 mL) was then added and the reaction mixture was further stirred for about 2.5 hours.

**[R-(R*,R*)]-2-(4-Fluorophenyl)-β,
δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-
[(phenylamino)-carbonyl]-1H-pyrrole-1-heptanoic acid, sodium salt (Atorvastatin Sodium)**

The pH of the reaction mixture obtained above was adjusted to about 12 by adding 10% w/v aqueous sodium hydroxide solution at 25-30 °C and the resulting mixture was stirred for about 6 hours at 25-30 °C. The progress of the reaction was monitored by HPLC. The pH of the reaction mixture was monitored and maintained at about 12 throughout the course of the reaction by adding 10% w/v aqueous sodium hydroxide solution. After the reaction was complete, the mass was filtered and concentrated to get the title compound as a white precipitate.

**[R-(R*,R*)]-2-(4-fluorophenyl)-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-
[(phenylamino)-carbonyl]-1H-pyrrol-1-heptanoic acid, calcium salt (2:1) (Atorvastatin
Calcium)**

De-ionized water (500 mL), methanol (200 mL), and methyl tertiary butyl ether (200 mL), were added to atorvastatin sodium obtained above and stirred to obtain a solution. The layers were separated. The aqueous layer was washed with methyl tertiary butyl ether(200 mL), and filtered through hyflo bed. The hyflo bed was washed with a mixture of methanol (25 mL) and methyl tertiary butyl ether (25 mL). The filtrate was warmed to 50 °C and its pH adjusted to about 10 with concentrated hydrochloric acid. To this mixture, an aqueous solution of calcium acetate (7.52 g) in water (275 mL) was added slowly in 1.5 hours at 50 °C. Some turbidity was observed at this stage. Methyl tertiary butyl ether (20 mL) was added. Some methyl tertiary butyl ether spontaneously evaporated at this stage. The mixture was heated to 80 °C to obtain a clear solution. The contents were stirred for 20 minutes at the same temperature and then allowed to cool for 1.5 hours. The contents were further cooled to 25 °C and stirred for 30 minutes at the same temperature and then filtered. The wet product was slurry washed with a mixture of methanol and de-ionized water (2:1, 100 mL) and filtered. The material was dried at 45 °C for 8 hours to yield 43.38 g of atorvastatin calcium. The XRD spectrum of the product mainly showed two very broad peaks.

Part B- Preparation of crystalline atorvastatin calcium form-I seed

Step I

Atorvastatin calcium (2 g) obtained above was suspended in de-ionized water (20 ml) and stirred for 20 hours at about 30° C. The suspension was then filtered and dried under reduced pressure at 40 to 45° C for 3 hours to get 1.9g of the product. The XRD spectrum of the product showed a change in pattern from that of the starting atorvastatin calcium. An increase in sharp peaks indicating increased crystallinity was observed.

Step II

Atorvastatin calcium (1.8 g, same as that used as starting compound in step I) and atorvastatin calcium (0.2 g, obtained from step I above) were suspended in a mixture of de-ionized water (34 ml) and methanol (6 ml). The temperature was raised slowly to 38 to 40 °C and the suspension was stirred for 16 hours at the same temperature. The suspension was then cooled to 35 °C, filtered and dried under reduced pressure at 40 to 45 °C for 4 hours to get 1.9 g of the product. The XRD spectrum of the product showed a change in pattern from that of the starting atorvastatin calcium. The XRD spectrum of the product matched with that of Form-I of atorvastatin calcium.

Example 12: Preparation of crystalline atorvastatin calcium form-II seed

A mixture of methanol (360 ml) and de-ionized water (240 ml) was added to a mixture of amorphous atorvastatin calcium (15 g) and crystalline atorvastatin calcium form I (15 g), the suspension was warmed to 45 °C slowly and stirred at the same temperature. The suspension became very thick after 24 hours and a mixture of methanol (180 ml) and de-ionized water (120 ml) was added to resume stirring. The suspension was warmed to 45 °C and further stirred at the same temperature for 24 hours and then filtered. The filtered solids were dried under reduced pressure at 70 °C for 48 hours to get 27 g of crystalline atorvastatin calcium. The XRD spectrum of the product matched with that of Form-II of atorvastatin calcium.

WE CLAIM:

1. A crystalline form R of atorvastatin hemi calcium and hydrates thereof.
2. Crystalline atorvastatin hemi calcium form R or a hydrate thereof having a powder XRD pattern substantially as depicted in FIG. 1.
3. Crystalline atorvastatin hemi calcium form R or a hydrate thereof having IR spectrum substantially as depicted in FIG. 2.
4. The crystalline form R of atorvastatin hemi calcium of claim 1 exhibiting an XRD spectrum comprising characteristic peaks at about 8.62, 10.16 and 19.32 degrees two-theta.
5. The crystalline form R of atorvastatin hemi calcium of claim 1 further comprising peaks at about at 3.6 , 8.24 , 18.12 , 18.36 , 20.44 , 20.82 , 21.22 and 23.82 degrees two-theta.
6. A process for preparing crystalline form R of atorvastatin hemi calcium and hydrates thereof comprising dissolving crude atorvastatin hemi calcium in a solvent system comprising tetrahydrofuran and methanol and recovering Form R atorvastatin hemi calcium or hydrates thereof.
7. The process according to claim 6 wherein crude atorvastatin is any of the polymorphic form reported earlier.
8. The process according to claim 6 wherein crude atorvastatin hemi calcium contains unreacted compounds, side products or other impurities.
9. The process according to claim 6 wherein mixture of crude atorvastatin hemi calcium and solvent system is heated upto reflux.

10. The process according to claim 6 wherein Crystalline form R of atorvastatin hemi calcium and hydrates thereof is precipitated by addition of an anti solvent.
11. The process according to claim 10 wherein an anti solvent is water.
12. The process according to claim 6 wherein Crystalline form R of atorvastatin hemi calcium and hydrates thereof is isolated by cooling the reaction mixture to a temperature of about 20 to 40°C.
13. The process according to claim 6 and 11 wherein tetrahydrofuran, methanol and water are in the volume ratio 1:1:4.
14. A process for the preparation of stabilized amorphous form of atorvastatin hemi calcium comprising dissolving crystalline Form R of atorvastatin hemi calcium and hydrates thereof in a solvent, and adding the anti-solvent to the resulting solution.
15. The process according to claim 14 wherein solvent is selected from the group consisting of ketones, esters, chlorinated hydrocarbons, cyclic ethers, alcohols, nitriles, dipolar aprotic solvents and mixtures thereof.
16. The process according to claim 14 wherein anti solvent is selected from the group consisting of hydrocarbons and dialkyl ethers.
17. The process according to claim 14, wherein an antioxidant is added to the atorvastatin hemi calcium solution to obtain stabilized amorphous atorvastatin hemi calcium.
18. The process according to claim 17, wherein an antioxidant is selected from the group consisting of butylated hydroxyanisole, butylated hydroxytoluene and tertiary-butylated hydroquinone.

19. A pharmaceutical composition comprising crystalline form R of atorvastatin hemi calcium or hydrates thereof along with pharmaceutically acceptable excipients, diluents and carriers.
20. A method for treatment or prevention of hyperlipidemia, hypercholesterolemia, Alzheimer's disease atherosclerosis, xanthoma and in synergism with other drugs for treatment of phytosterolemia lipase deficiency and the like, which comprises administering to a patient in need thereof, a therapeutically effective amount of Crystalline Form R of atorvastatin hemi calcium or hydrates thereof.
21. The use of crystalline form R of atorvastatin hemi calcium and hydrates thereof in the manufacture of a medicament for the treatment or prevention of hyperlipidemia, hypercholesterolemia, Alzheimer's disease, atherosclerosis, xanthoma and in synergism with other drugs for treatment of phytosterolemia lipase deficiency and the like.
22. A process for preparing crystalline form R of atorvastatin hemi calcium and hydrates thereof comprising dissolving crude atorvastatin hemi calcium in a mixture of tetrahydrofuran and methanol, and precipitating with water to obtain crystalline form R of atorvastatin hemi calcium.
23. The process for the preparation of Crystalline Form R of atorvastatin hemi calcium or hydrates thereof as herein described and illustrated by the examples herein.

Dated this 16TH day of March, 2005.

For Ranbaxy Laboratories Limited


(Sushil Kumar Patawari)
Company Secretary

05 23 05
ABSTRACT

CRYSTALLINE FORM OF ATORVASTATIN
HEMI CALCIUM

The present invention relates to novel crystalline form R of atorvastatin hemi calcium salt and hydrates thereof useful as pharmaceutical agents, to methods for their production and isolation, to pharmaceutical compositions which include novel crystalline form R of atorvastatin hemi calcium salt and hydrates thereof and a pharmaceutically acceptable carrier, and to pharmaceutical methods of treatment.

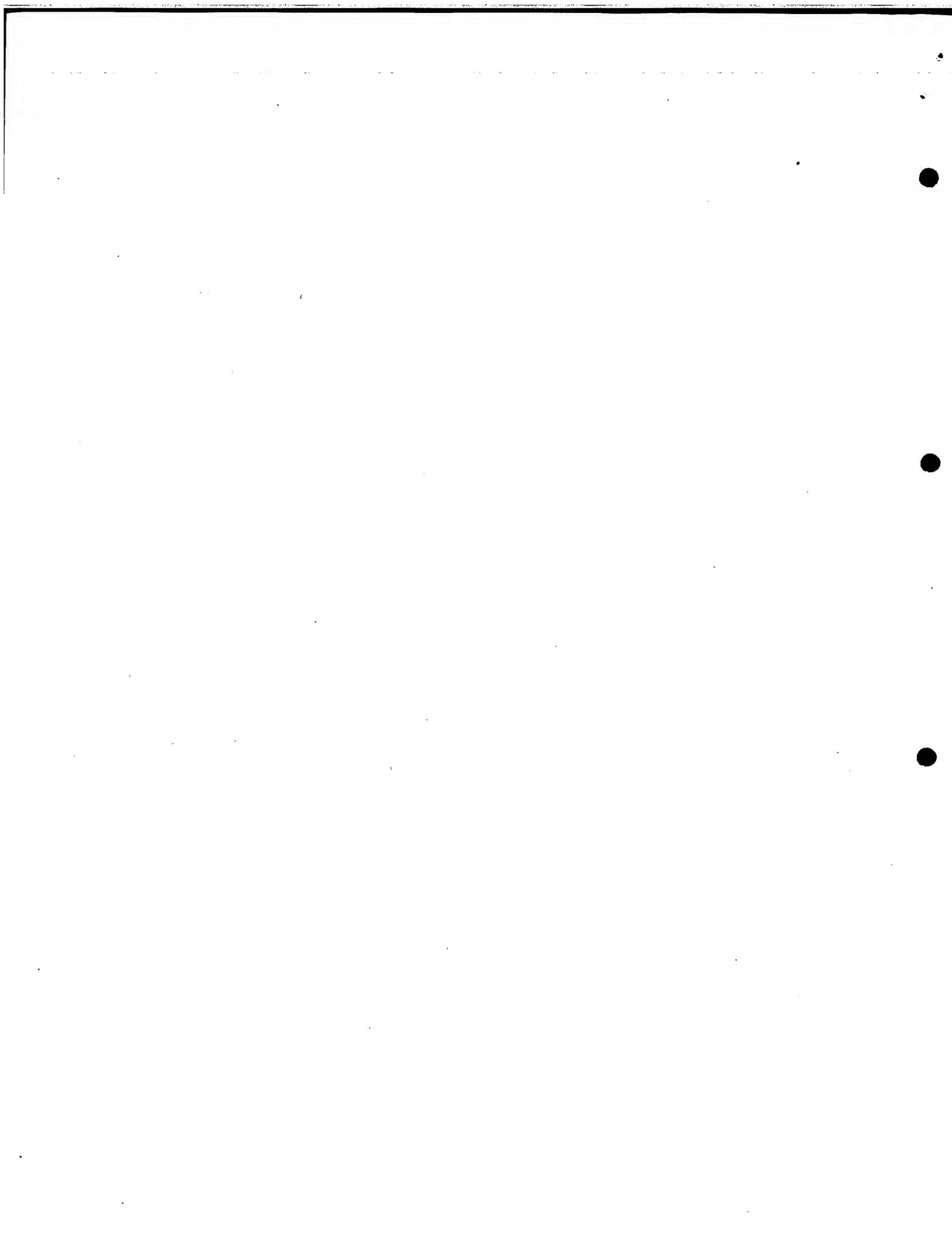
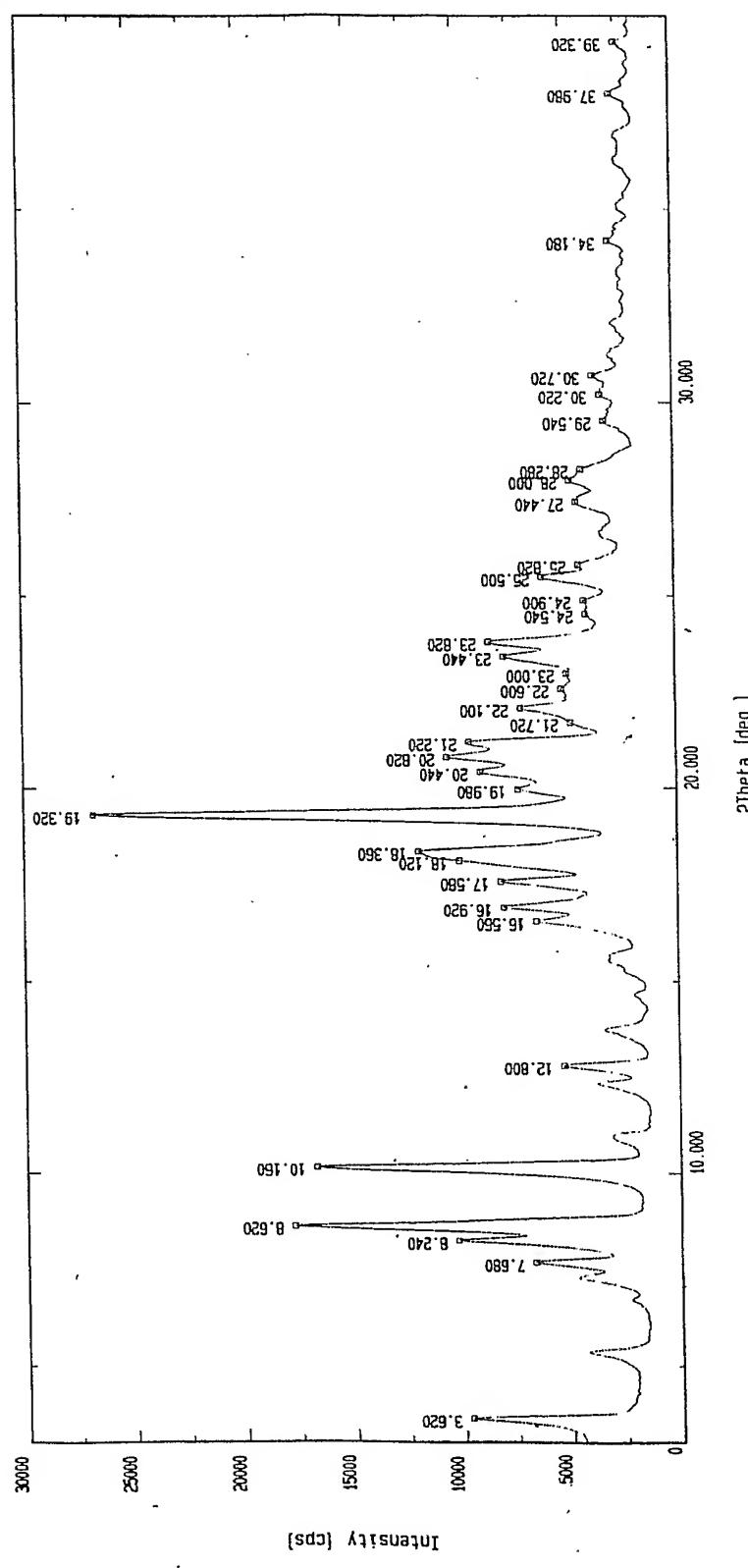


FIGURE 1



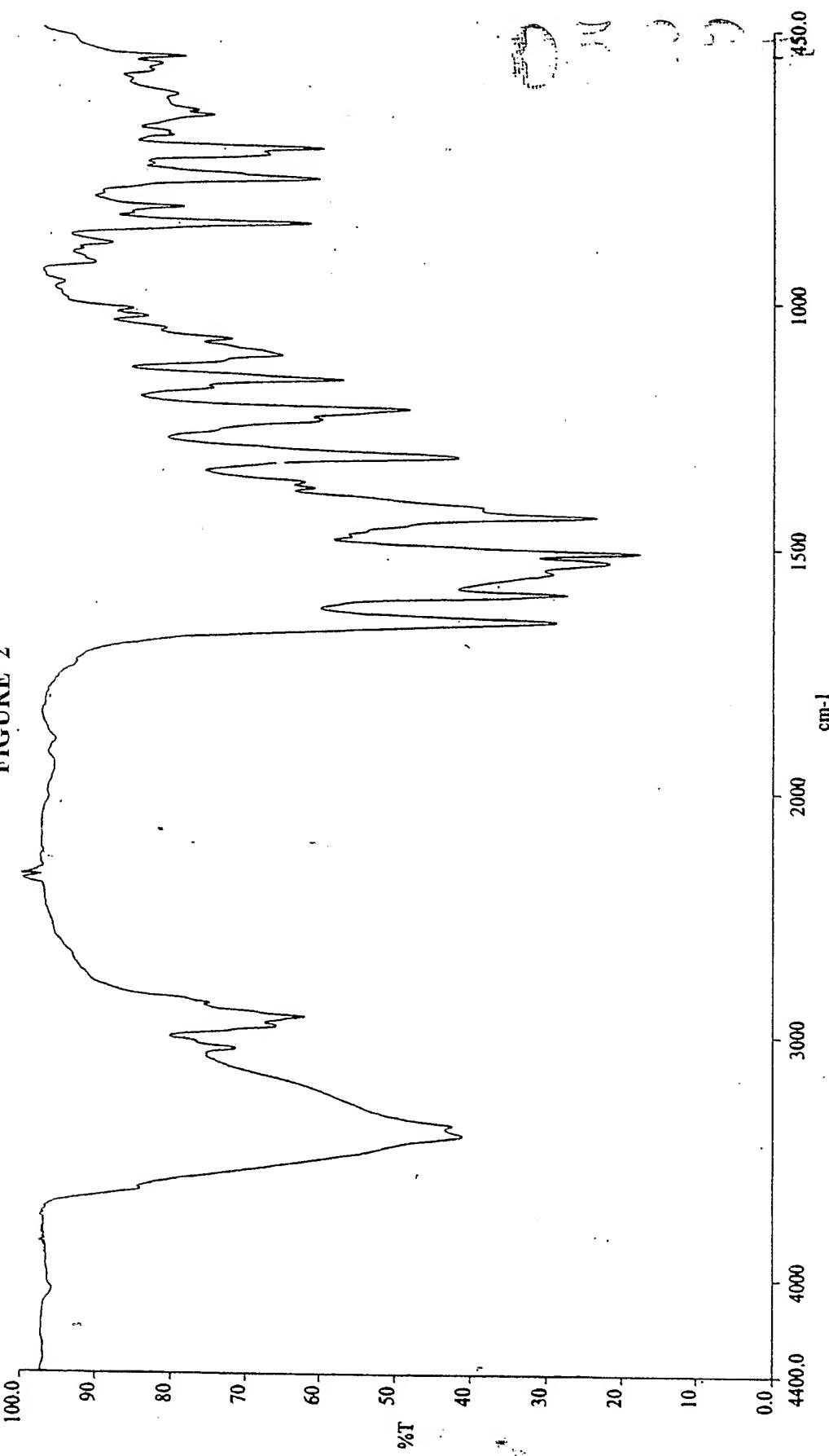
For Ranbaxy Laboratories Limited
S.K. Patwari
(Sushil Kumar Patwari)
Company Secretary

Ranbaxy Laboratories Limited

Application No.

No. of sheets = 03
Sheet 01 of 03

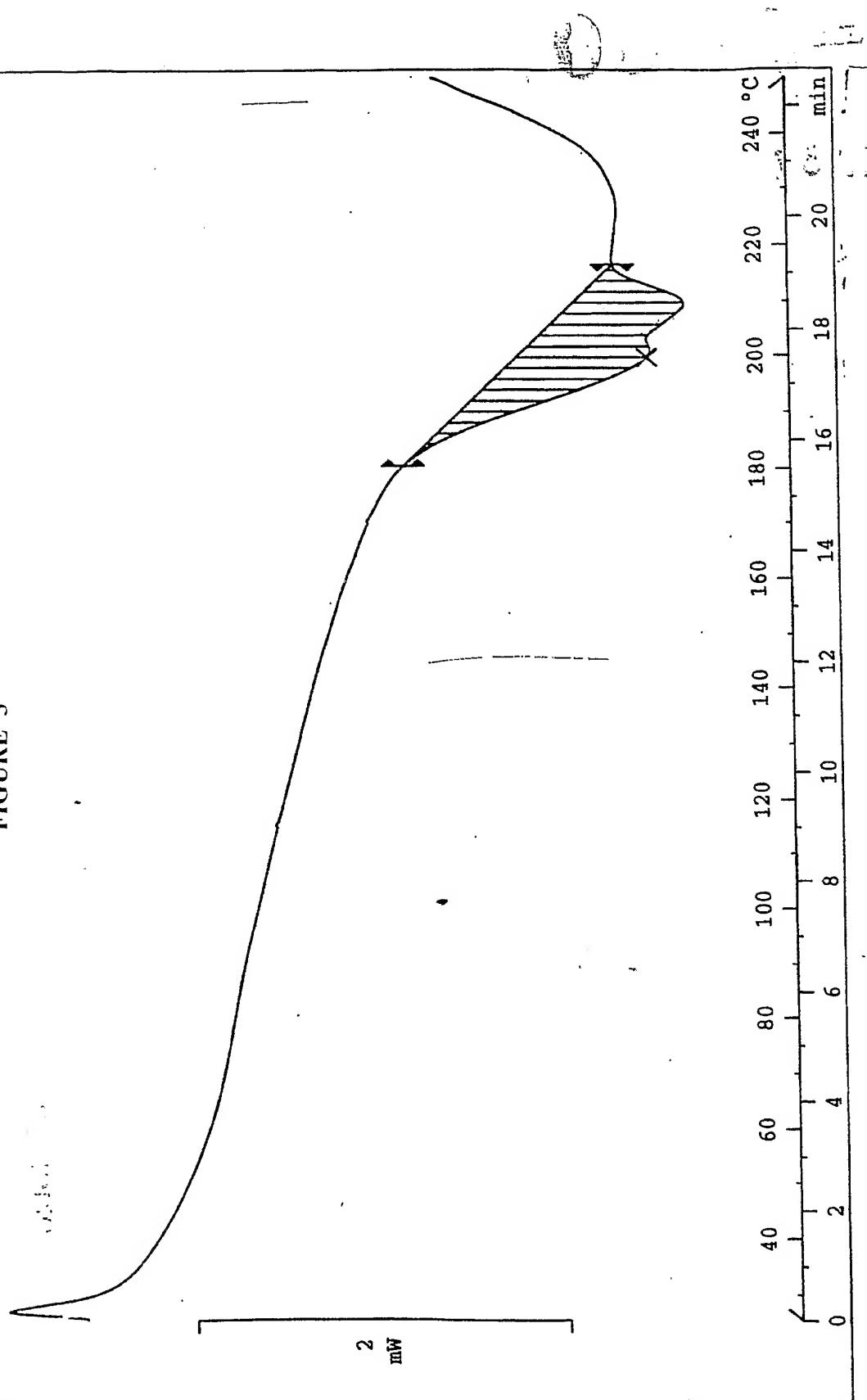
FIGURE 2



For Ranbaxy Laboratories Limited

Sushil Kumar Patwardhan
Company Secretary

FIGURE 3



For Ranbaxy Laboratories Limited
Sushil Kumar Patawari
(Sushil Kumar Patawari)
Company Secretary

